The Voice of the Patient

A series of reports from the U.S. Food and Drug Administration's (FDA's)
Patient-Focused Drug Development Initiative

Patient-Focused Drug Development for Alpha-1 Antitrypsin Deficiency

Public Meeting: September 29, 2015
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Center for Biologics Evaluation and Research (CBER)
U.S. Food and Drug Administration (FDA)

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Introduction

On September 29, 2015, FDA held a public meeting to hear perspectives from patients with Alpha-1 Antitrypsin Deficiency (AATD), their caregivers, and other patient representatives. The meeting enabled discussion on the impact that AATD has on patients' daily lives, as well as discussions on currently available therapies, and patient considerations on drug development. FDA conducted the meeting as part of the Agency's Patient-Focused Drug Development initiative, an FDA commitment under the fifth authorization of the Prescription Drug User Fee Act (PDUFA V) to more systematically gather patients' perspectives on their condition and on therapies that are available to treat their condition. As part of this commitment, FDA is holding at least 20 public meetings over the course of five years, each focused on a specific disease area. More information on this initiative can be found at http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm326192.htm.

Overview of Alpha-1 Antitrypsin Deficiency

Individuals with AATD have low serum levels of alpha-1-antitrypsin (AAT, also known as alpha-1 proteinase inhibitor (A1-PI)). They have an increased risk of developing a form of chronic obstructive lung disease called emphysema, caused by damage to the small air sacs in the lung, and, less frequently, liver disease. AATD occurs in approximately one in 5000-7000 individuals in North America.

There are different genetic forms of the disease, but even among people with the same genetic form of the disease and similar levels of AAT in their blood, there is tremendous diversity in clinical severity. A substantial percentage of individuals with severe AATD never develop symptomatic lung disease during their lifetimes. Others may develop the first signs and symptoms of lung disease between the ages of approximately 25 and 50 years, or older. Some AATD patients with emphysema have symptoms of asthma. Progression of emphysema in AATD may lead to respiratory failure, a need for lung transplantation, and eventually death. The only specific medication approved for raising the blood levels of AAT in severe AATD patients with emphysema is weekly intravenous treatment with A1-PI (Human), purified from human plasma.

Severe AATD patients may also develop liver disease as infants, during childhood, or as adults. The severity of liver disease varies widely among affected patients. Currently, no specific therapy for AATD-related liver disease is available other than liver transplantation, so the focus in these patients is on the prevention and management of other types of liver damage.

Meeting overview

This meeting provided FDA with the opportunity to hear directly from patients and caregivers about their experiences with AATD and its treatments. Approximately 850 AATD patients or patient representatives actively participated in the FDA's Patient Focused Drug Development meeting, either in-person, or through the live webcast. Others in attendance included representatives from FDA, other federal agencies, industry, healthcare professionals, and patient organizations. According to the responses to polling question (Appendix 3) of patients participating in-person, approximately half had emphysema, half reported having liver disease, most were in the 50-64 age group, and the ratio of males to females was 1:1. Notably, most participants appeared to be highly connected through social media, research, and support foundations, and were very familiar with drug development and regulatory processes.

Meeting discussions focused on two key topics: (1) disease symptoms and daily impacts that matter most to patients, and (2) patients' perspectives on current approaches to treating AATD. The questions for discussion (Appendix 1) were published in a Federal Register Notice (80FR 31048) (https://www.gpo.gov/fdsys/pkg/FR-2015-06-01/html/2015-13063.htm) prior to the meeting. For each topic, a panel of patients and caregivers (Appendix 2) shared comments to begin the dialogue. Panel comments were followed by a facilitated discussion inviting comments from other patients and caregivers in the audience. An FDA facilitator led the discussion, and a panel of FDA staff (Appendix 2) asked follow-up questions. Participants who joined the meeting via live webcast were able to submit comments throughout the discussion, and their comments are incorporated into this summary. In-person and web participants were periodically invited to respond to polling questions (Appendix 3), which provided information on the demographic makeup of participants, as well as the number of participants who shared a particular perspective on a given topic.

To supplement the input gathered at the meeting, patients and others were encouraged to submit comments on the topic to a public docket[1] , which was open until November 30, 2015. Twenty one comments were submitted: two from a patient organization, and 19 from individuals. The comments received via the public docket have been incorporated into this summary.

More information on the meeting, including the archived webcast and transcript is available on the meeting webpage:
http://www.fda.gov/BiologicsBloodVaccines/NewsEvents/WorkshopsMeetingsConferences/ucm435242.htm

[1] A docket is a repository through which the public can submit electronic and written comments on specific topics to U.S. federal agencies such as FDA. More information can be found at www.regulations.gov.

Report overview and key themes

This report summarizes the input provided by patients and caregivers at the meeting. It also includes a summary of comments submitted to the docket, beginning on page 22. To the extent possible, the terms used in this summary to describe specific lung or liver disorders, health effects and impacts, and treatment experiences, reflect those of participants or docket commenters. This report is not meant to be representative of the views and experiences of the entire AATD patient population or any specific group of individuals or entities. There may be symptoms, impacts, or treatment experiences that are not mentioned in this report.

The input that FDA received from this meeting highlights the diversity of AATD symptoms, the range of disabilities and comorbidities that accompany the disease, and the challenges that patients and caregivers face in dealing with this disease, while striving to lead a normal life. Several key themes emerged from their input:

- Participants with ATTD spoke about their ongoing struggle with shortness of breath while exercising or even at rest. They told of wheezing, productive coughing, frequent exacerbations, exhaustion and anxiety. Some participants, with liver disease, described their experiences with bleeding, failure to thrive, and complications caused by medications received after liver transplantation.

- Participants stressed that one of the biggest challenges to effective therapy was the cost of augmentation therapy and insurance limitations. They also mentioned the need for optimal dosing strategies, and the narrow range of treatment options, especially for liver-affected individuals. Other issues they cited were access to treatment, side effects, and early recognition and identification of the disease and its symptoms by emergency room and primary care physicians who were unfamiliar with AATD.

- Throughout the discussion, many participants described how AATD can pose social, educational and career challenges. They emphasized the need for treatments that allow patients to pursue activities such as travel and social activities. Participants shared that more attention should be paid to the social, psychological and financial impacts of AATD. Many participants shared the importance of building awareness and education about AATD and its treatments among physicians and the general public.

- Participants acknowledged that significant advancements in treatment have occurred over time, allowing patients to become more independent and to have more control over their lives. They cited advancements such as augmentation therapy, improved oxygen delivery systems and transplantation. Nevertheless, participants expressed their desire for safer,

better, and more innovative ways to treat AATD. Many participants indicated that options for treatment are not ideal, and are often accompanied by discomfort or risk.

- Participants shared that the ideal treatment would be a cure, through gene therapy or through a lung or liver transplant, with no accompanying side effects or need for continuing the maintenance of therapy. Barring that, participants want safe, effective, potent, inexpensive, very long acting, and easy to administer products.

- Many meeting participants have participated, or would be willing to participate in a clinical trial, but a substantial number said they would be willing, but only if they could also remain on their current therapy.

Topic 1: Disease Symptoms and Daily Impacts That Matter Most to Patients

The first topic of discussion at the meeting focused on patients' experiences with AATD symptoms. In particular, FDA asked participants to discuss the symptoms and complications of AATD and the resulting impact that these health effects exert on their daily lives. Six panelists provided comments to start the dialogue. They included a man with Chronic Obstructive Pulmonary Disease (COPD) and AATD that affects his lungs, a man who has children with AATD, a man with AATD that affects primarily his liver but also his lungs, and two men and a woman with ATTD that affects their lungs. These participants described the daily challenges they face with their respective conditions, and shared the significant fears, frustrations, and stresses that they or loved ones experience because of their conditions. Their testimonies provided a rich context for dialogue over the course of the meeting, and nearly all patients and patient representatives in the audience indicated (by a show of hands) that their or their loved one's experiences were reflected in the panelists' comments.

Perspectives on symptoms

Shortness of Breath

When queried on the impact of their disease symptoms (Appendix 3, question 5), all lung affected participants cited shortness of breath as having the most significant impact on their or their loved one's daily life. One participant shared that, "Shortness of breath has definitely had a huge impact on my life. Starting at the age of 35, I was no longer able to work, I was no longer able to do the activities that I enjoyed with my children, and I was no longer able to be intimate with my partner. Very sad to be old at a young age." Another commented, "My most severe symptom or my most obvious symptom is the shortness of breath on any exertion, even limited exertion and it's when you can't breathe nothing else matters."

Chronic Coughing, Lung Spasm

Many participants described symptoms of chronic coughing, lung spasm, sometimes triggered by vapors, dust, or smoke. One participant shared her experience shopping "I can't shop freely at stores. . . because some stores have inadequate ventilation and sometimes the outgassing of plastics and material prevent people from walking through the whole store and making their own choices." Another participant described her reactions to odors or smoke. "If I walk through a door where someone has been smoking outside of the designated smoking area where cigarette smoke lingers, at the perfume counter, [or] walk-through the flower shop. . . anywhere fragrance is, can cause a very bad spasm of the alveoli in my lungs and brings on a great shortness of breath crisis."

Liver Disease

When queried, over two thirds of participants with liver disease cited abdominal pain and swelling as being the most significant symptoms that affected their daily lives. In addition, a parent shared his concern about his son's liver disease. "It's a very difficult process to be worried about your kids and their liver disease. . . . [My son] would be running around all over this room right now. But he has a failure to thrive. At seven years old. . . he weighs 39 pounds. . .He's not even on the growth chart."

A few participants shared their experience with bleeding caused by AATD-associated liver disease. One participant said of her mother, "She started vomiting in the middle of the night and then she realized that she wasn't just nauseous. (She gets nauseous a lot). . . that it was blood. . . She got [to the hospital] and they banded her and it actually worked out really well. But she was very lucky. The physician who admitted her told her that it's an 80% mortality rate for that type of bleed."

Another participant whose husband had had liver disease said, "Alpha-1 liver disease may be a very small part of the Alpha-1 patients except it progresses very, very quickly. Somebody can be diagnosed and they can be dead in six months with AATD liver disease."

Disease Symptoms Exacerbated by Aging

One participant shared his experience of AATD as he aged, saying that "as you age, you have more shortness of breath and there are more and more things that you can't do anymore. Golf, I miss that a lot. I say I can still hit the ball out of a sand trap, but I can't get myself out of the sand trap."

A participant commented that "I've noticed with the passage of time, a decrease in muscle mass. And although I work out quite a bit and do strength training, I still don't get as much bang for my buck is I did when I was younger. . . . Improving muscle mass would increase my functionality, so I think that's another important effect of aging."

Another participant described an increased urgency to go to the bathroom. "As you age, things loosen up a little bit. . . .One thing in particular is being close to a bathroom if you're real short of breath. . . .When you have a choice to breathe or go, sometimes you just go and it can be pretty embarrassing, especially if you're on an airplane (or not on an airplane)."

One participant with liver disease described his changes in symptomatology over time. He was diagnosed as an infant and took a special formula that often caused projectile vomiting. Between the ages of 16 through 24 he did not require any medication. "And then when I turned 24 everything just went downhill. My liver decided it was not working with me anymore. I then needed various medications to manage the complications of liver failure. I was on diuretics for the ascites; at one point… they tapped 10 liters of fluid out of my left lung. So not breathing is not fun. . . . I had insomnia very bad, and cramping. I was on a low-sodium diet, and it just completely changed my personality until I received the transplant when I was 25 years old. . . Some of the negative aspects of my treatment, the anti-rejection medication that can be really hard on your kidneys so I could be looking at a kidney transplant eventually. . . .[I have a] higher risk for diabetes and skin cancer."

Perspectives on the overall impact of AATD on daily life

Anxiety/Depression/Stress

Anxiety and depression were cited by responding participants (Appendix 3, question 5) as the third symptom having the most serious impact on their daily lives. One participant stated that "For those of us with Alpha-1, daily stress is a factor that impacts our lives on a daily basis. Environmental issues, financial concerns, the lack of family nearby to assist with daily needs. All this adds to a level of anxiety for many of us." Another participant shared his concerns, "There's no cure for AATD. There is no treatment for the [lung] aspects of this disease or for the liver aspects of this disease. My father died of liver failure and I'm challenged by the thought of what my family's future will be." On a similar note, a participant added, "What worries me most is the loss of my independence and inability to care for myself and to be an active participant with my family. The loss of the control of my choices for treatment that are limited, either due to not being there, insurance issues, etc."

Career Choices

A number of participants remarked on their experience of being forced to give up work. One recounted, "The reason that most of us don't mention our work is that we have become unable to work and oftentimes are forced into disability." Another participant shared that, "I had a very high executive position for a very big company and I was relieved from my employment because my oxygen tank bothered the upper echelons of the business." Said another, "Before the transplant I was a veterinary technician and I can no longer do that because of the high risk of infection."

A participant told about his career change after discovering he had AATD "I owned two businesses, I had two kids, very active in the community. . . .Well, with being on oxygen 24/7, living at eight thousand feet is not conducive. Put my house on the market, hired a great general manager, and took early retirement."

Travel

Many participants shared how AATD patients face many obstacles on a daily basis such as stairs, walking from parking lots through malls and stores; carrying bags, portable oxygen and luggage; and travel in general. One commented, "Handling luggage throughout the trip, navigating through airports with oxygen equipment and dealing with the logistics of rental cars or transportation at the destination create so many issues that make staying at home an attractive option." Said another, "Travel is difficult. It can be a nightmare to travel by air." Another participant spoke about the challenges he faced in traveling by air. "Inhalers ought to have covers on the mouth pieces that are antimicrobial . . . .You're going through the airport check-in. . .and they put your inhaler in this little box. Look in that little box; it's got stuff growing in it and you want me to use that as a rescue inhaler and I've already got Aspergillus. . .and God knows what else's growing in my lungs."

A participant shared, "I use supplemental oxygen when I sleep when I exercise and when I fly or at altitude. Being able to manage the logistics of having supplemental oxygen. . . has been a real challenge." He mentioned having to be sure to have enough oxygen, the right liter flow, enough batteries, and whether one would be able to get oxygen at the final destination.

One participant described the difficulties of travel in the winter in Michigan. "If you don't have an automatic start, [you have to] let your car warm up, scrape your windows. That's all you can do, you have to go back and sit down for 20 minutes; it's a tough way to go."

Sports and Exercise

A participant commented, "My inability to keep up with peers, play sports, do aggressive exercise, carry heavy objects and even walk and talk at the same time are a constant reminder of my condition. . . . My first dramatic breathing problem was when I was scuba diving in the Red Sea; I thought I was going to die."

A participant described his decline in his ability to participate in sports over time "I was a multisport athlete. . .I did a lot of stuff. . .and over the years I stopped playing competitive tennis at age 40; I stopped playing competitive baseball at 47; I stopped walking hills with a pack going hunting at 52. You know, these are things that are part of identity, things that I won't get back. On the other hand, golf is looking pretty good for me. You know, other opportunities arise. . . I do see this as the one door closing but two more opening up. And I'm optimistic that as long as I engage myself in the process, there'll be more for me out there."

Another participant shared that "One activity that I've had to give up completely is dancing. Although I do exercise, I can no longer. . . exercise at the level that I previously did and this not only affects my physical well-being but also my emotional well-being insofar as dance was one of the ways that I expressed myself."

Family Life

A common theme expressed by many meeting participants was the effect that AATD can have on the daily life of a patient's family as well as that of a patient. One participant shared her experience with her mother who has severe liver disease, is awaiting a liver transplant, and could not participate in preparing for the participant's wedding. "She is not able to help at all with the wedding. . . .We planned our wedding for year and a half, and she wanted to do so many things for us and make centerpieces and be there on the day and be there in the morning and be there when I put on my dress, and she couldn't. She was in her room until right before the ceremony and she was just exhausted the whole time."

A father shared "As a young father of two active sons and as an elementary schoolteacher, educator, and principal, my ability to participate in activities that active children like to do was severely impaired. . . .Engaging in sports, going on family trips and vacations that required any type of walking, climbing stairs, etc. not only presented challenges and careful planning, but also resulted in severe anxiety. . . . Each day had to be carefully planned and orchestrated. Routine household chores such as mowing the lawn, taking out the trash, completing small fix of jobs, even the simple task of changing a light bulb became too difficult or challenging to do. . . Eventually I required supplemental oxygen which presented additional challenges for the workplace as well as for daily living."

Similarly, another father with a young family shared that, "You've got a kid, a six-year-old, and all of a sudden, bang,. . . you find your world is turned upside down. Everything from savings, what you're doing in your future, everything has to be revamped because you have a sick child with liver disease, or you're 40 years old, and you find yourself diagnosed with AATD. . . and you can't go back to the work that you were doing and having choices to make, change of location, what do you do? It's very difficult and the spouse, or the mate, or the partner all of a sudden has to take the slack out and it can be a very difficult strain on the relationship or the marriage."

One participant shared that "The thing I missed most during my early years of lung disease with not being able to play with my daughter. We'd go to the beach, I was always the dad that sat back and watched mom play with the kid. . . . I tried to go out and play with her. . .and I'd be gasping for air."

A participant described the challenges he faced growing up "AATD has affected my life from day one. . . . I couldn't join the military when I turned 18. I couldn't follow my father's footsteps. Knowing that it could eventually affect my children's children is really hard. . . .I also just want to thank my parents. I can't imagine how they deal with stuff being the parent of an Alpha. To all parents, thank you."

One caregiver described how he "did 30 years of active duty in the military, been in more war zones than I know of, got two purple hearts, and I'll tell you, there is nothing worse than sitting there watching [his wife] gasp for air and try to breathe. . . .You know, it's tough to stand there and do nothing, can do nothing."

Intimacy

Many participants commented that AATD affected their sexual life. One participant shared "Sex is hard, but I'm not giving it up." Another commented "Sex is definitely one of the things that has gone away with the inability to breathe. It's not very romantic to be with an oxygen tank and let's put it up and let's put it down, and, oh my God." A third participant shared, "One of the most difficult things for me to handle, it was during times of intimacy. You know, it's really hard to be in the moment when you're wheezing. I just can't do it, you know. Arrangements have to be made."

Social Life and Support Groups

A caregiver described her husband's bronchiectasis. "He would cough. He missed years of our kids' and grandkids' lives because he couldn't go to plays or movies or soccer games or anything

because he would cough and it would be so disruptive to them. In fact, he coughed so much he wound up with bilateral hernias."

Another participant with liver disease remarked "what I have missed is my childhood. I was diagnosed with Alpha at 10 weeks old. [Because of transplant operations] I missed all my friends' parties, functions, school events, field trips."

Many participants expressed gratitude for the help that they have received from support groups. One participant said "Involvement in the Alpha-1 community has really changed my life completely. . . given me an opportunity to work with our Alpha-1 community and build a research program and make certain that we take care of each other."

A participant spoke about how important it was to be involved with a support group "You know, we're from different places but we share this common thing and I see it as hope." He also shared his appreciation of his caregivers. "My relationship with my infusion nurses. . .they are like my dear friends. I'm not so happy when they stick me, but I know at the end of the day it's all for my own good and they want nothing but my best interest."

One participant commented that, prior to lung transplant, the most effective treatment was the assistance of AlphaNet, a not-for-profit health management corporation. The AlphaNet coordinator was instrumental in "making sure that I had my vaccines, making sure that I was keeping my doctor appointments, making sure that I was doing my augmentation therapy on a weekly basis and staying on schedule, and making sure that if I was taking a trip, I knew what was needed to do as far as oxygen adherence was concerned."

Topic 2: Patient Perspectives on Current Approaches to Treatments

The second main topic of discussion focused on patients' experiences with therapies used to treat their or their loved ones' condition. Six panelists provided comments to start the dialogue. They included a woman with lung and, potentially, liver disease; a woman with lung disease; two men with lung disease; a mother whose son had had liver disease; and a man with liver disease. Panelists shared their and their children's experiences with a variety of treatment regimens, including prescription medications and lifestyle changes.

The following is a summary of the treatment perspectives described through comments made at the meeting, on the webcast, or submitted to the public docket. A few key themes emerged during the second topic portion of the meeting, most notably:

- Products are needed which will stop AATD liver and lung disease at an early age, remain effective for a longer time, are less expensive, easier to use, and/or provide a cure.

- Physicians should become better educated about AATD associated disorders and be more attentive to a given patient's needs and level of knowledge.

- More information is needed to obtain correct dosage and dosing of augmentation therapy with AATD.

- Many participants are willing to join clinical trials that offer additional therapeutic options, but not at the risk of diminishing or stopping their current treatments.

Much of the discussion in this part of the meeting involved participants' concerns about receiving the appropriate treatment at the right time and in the right amount.

Perspectives on current treatment for conditions or symptoms

Recognition and Treatment of AATD

Many participants expressed concern that physicians often did not recognize, understand, or appropriately treat ATTD. As one participant commented, "The group that aren't here are the people that don't know they have this disease. . . .I've run across 30 to 40 [physicians] in the last six months who have never heard of this disease. . . .We do not have any regular testing in this country despite the fact that lifestyle changes and environmental changes will make a bigger difference in the long term prognosis than any treatment currently available. . . . There's 100,000 people out there with lessened life expectancy because we don't do basic education and basic testing for this disease that we already know how to do, that don't require inventing new drugs."

Another participant described how he was misdiagnosed many times, depending on the situation in which he found himself. "When I went and presented with breathlessness at an urgent care center in my workout clothes, it was exercise-induced asthma. . . .When I was in Vegas with some friends. . .I presented in the hospital with breathlessness and rather than run any vitals they proceeded to question me on drug use and what I had done that night that would cause that."

A mother commented on the challenge she faces in dealing with several physicians to care for her children who have AATD. "A challenge for me has been having multiple specialists who are very good in their field but don't necessarily know how everything interacts with each other, and maybe aren't [educated] in AATD to know how that affects the big picture of their lives."

One participant described the need for better education of physicians to treat AATD "My doctor finally acquiesced, and I'm on oxygen for sleeping, and that's helped a great deal after being

tested. Why did I have to find out for myself that oxygen has transformed my life when it comes to exercise, it's transformed my life when it comes to yard work, to exertion, [and to] sex?"

Early Diagnosis

Several participants expressed the need for a protocol to identify and diagnose patients earlier. As one said "We desperately need a widespread and standard testing protocol, because that is the key to identifying the complete breadth of our problem; the number of Alphas currently out there." Another said "We, as a community, need a standard testing protocol developed and implemented to enable earlier diagnosis." A mother commented that she regretted that her children weren't diagnosed at an earlier age "The biggest thing for me would have been if my kids were tested as infants, because they would have come up as MZs. . . . I probably wouldn't have moved to Colorado; I would've stayed in Minneapolis, because there was no oxygen at 8000 feet."

A participant shared his experience with a new test for identifying patients with AATD "In my travels in speaking about AATD all across the country, I've met with parents that have had their children's livers biopsied, have had surgeries, and it's really a shame because in this day and time we have a finger-prick blood test that will identify AATD. The pediatric community needs to get onboard and look for AATD by doing a simple blood test."

Obtaining Treatment

Many participants commented on their reluctance to go to a hospital or emergency room. One participant said that many people avoid the hospital "because of bacterial infections, especially methicillin-resistant staph aureus. Some feel that ERs are very dismissive. . . . Other people try to keep a supply of antibiotics and prednisone, working with their doctor to have it available." Another participant shared her experience in an emergency room, where the physician did not believe her when she told him that she had AATD because "it's super rare", and her treatment for a pulmonary embolism was therefore delayed.

One participant explained, "I think part of the reason we do not go to emergency rooms is because we're so proactive and we're aware of what our conditions are. We take a lot of our own treatment and we go ask the questions. We contact the physicians. . . and even to have to be sick and go to the doctor or go to an emergency room, you have to worry again about your oxygen and what's going to happen when you get there and how long are you going to have to sit."

A number of participants shared their difficulty in getting treatment because of insurance limitations. One participant commented, "I want to preserve lung function now; why do I have

to get sicker before I can have pulmonary rehab? I've never understood that but my insurance won't pay for it. The doctors say, 'No, I can't prescribe it because your insurance won't cover it.'"

Cost

In response to polling questions, a very large proportion of participants, both in the meeting room and on the web, expressed concern about the costs of treating AATD. One participant shared his experience "The costs financially, the cost of expectations having to be modified, I never fully realized the cost of one's quality of life and changes that have to be made in order to adapt -- in the cost of a shortened life, of a life never fully realized. . . . Financially we know there's heavy costs with being diagnosed with AATD. The therapy has increased 300% in 20 years. An inhaler can be a 30 dollar co-pay, or it can be a 90 dollar co-pay, or 120 dollar co-pay depending upon what tier you're on."

A number of participants advocated that the cost of augmentation therapy should be balanced against the cost of having to treat a patient who has not received augmentation. Said one participant, "If people are not on augmentation, if people are not using their medication, and have multiple exacerbations, multiple ICU stays, those costs are never stacked up against augmentation, and. . . if you did that you would see that providing the therapy is the most cost-effective way to go."

Current Augmentation Therapy and Other Treatment Options

Several participants spoke about their experience with different kinds of therapy. One participant described that, "A year and a half ago [my doctor] gave me sodium chloride 7% for nebulization and I mix that with my albuterol and it helps bring everything up without all the fighting."

Another said, "I've just recently been having great success with a really old drug theophylline, which is a pill form of albuterol and it's really helped me out. . . .I'm not sitting five different times during the day with a nebulizer; it allows me to live life a little bit easier."

The treatment plan of one participant included "weekly intravenous augmentation therapy, daily use of long acting bronchial dilators, inhaled and nasal corticosteroids, nebulizer solutions, and over-the-counter products to relieve congestion in my sinuses and my lungs. Several times each year, right around spring and fall, I have prolonged exacerbations leading to antibiotics and prednisone."

One participant shared that to say infusing AAT has "been disruptive to my work schedule is just about the biggest understatement possible. My infusion from beginning to end [including travel time] takes a pretty hefty time slice out of my day."

Participants discussed how treatment options for AATD can have their own hazards, side effects, and unintended consequences. For example, one participant reported that, "I find that prednisone has been very helpful. The problem is the side effects are not very pleasant. . . .It contributes to [hyperactivity]. . .When I do have to take [it] over a long period, I have developed osteoporosis over time and osteoporosis can disqualify one for a transplant. And it's a choice of would I want to continue with high-dose prednisone? I have had my prednisone decreased [and]. . .it is very helpful in exacerbations."

A participant shared that a complication of his taking corticosteroids was a "nasty case of thrush."

Dosing

A number of participants expressed concerns about determining and receiving an effective dosage of their medications. A participant shared "We need to know what dosage we should be on to be effectively treated. If I'm on 60 mg or less I'm sick every time I get on an aircraft. It's critically important that we address that question once and for all."

Another participant called for dosing counters on all inhalers. "There are still inhalers that don't have counters on them. I mean, how the hell am I supposed to tell if it says I have 200 inhalations; am I going to sit there and tick each one off in my diary every single day? No."

Lung Transplant

A number of participants shared their very positive experience with lung transplant. One participant commented "I had a lung transplant four years ago, and my life has totally changed. I'm doing everything I dreamed of." Another said, "It's just night and day, going from oxygen." One participant said about his father who had a lung transplant, "Now, he's Superman again, and he has that with his grandkids. . . . So I'm glad that we have transplantation, but the impact of getting to that point is tough on kids and tough on the family."

Other participants described difficulties that they have had after a lung transplant. A participant shared that even after a lung transplant he still continues "on weekly infusions to keep my new lungs protected. I have ongoing concerns about the possibility of liver disease, organ rejection and the future health of my family and grandchildren who are affected by this condition."

Another participant strongly discounted the perception that a transplant of a lung or liver is curative "A transplant is not lasting, and it's not simple. It's life encompassing to maintain and it certainly won't prevent me traveling down that road of progressive disease with AATD."

A participant commented on the death of her husband after a lung transplant "Transplant doesn't always go as easy as it is supposed to. . . So what a transplant has done for my daughters is. . taken their father from them."

Liver Transplant

One participant shared his observations about the benefits of a liver transplant "So far the treatment with the transplant has been very well; it's working for me very well. I'm currently four years post- transplant and I've had no major complications. Pre- and post-transplant for me were like night and day. . . . My color - I was so yellow before the transplant. I wasn't the same person. And then after transplant, it was like a switch went off. I could do all the things I wanted to do. I could mountain bike and play softball, and hike and it was really just amazing."

Several participants commented on the challenges they or their loved one faced after a liver transplant. Said one, "Now I'm immunocompromised because of the transplant so I have to take antirejection pills. Remembering those can be a pain sometimes, every 12 hours, but a small price to pay. It's also difficult when I have a little toddler running around, and he touches every germy thing in the world so I have to catch whatever he's running around with."

A mother spoke movingly about the failure of a liver transplant to save her son from liver failure. "The hardest aspect of the diagnosis was that there was literally nothing to offer him. Our thoughts over and over were how can we live in this day and not have some sort of treatment to give. How can transplant be the only offer to fix this? How can it be that the best hope is him not to get sick and stay on vitamins?. . . The treatments did not work. He continued to get sicker as his liver failed. By the time he got to transplant he was on 13 medications twice a day."

Non-Drug Therapies

Meeting participants described therapies that they use in addition to, or in substitution of augmentation therapy or organ transplant. These therapies included:

- Exercise: A participant said that "I've been actively involved with an exercise regimen for over 30 years now and have come to the conclusion that a regular and intense workout with cardiovascular and resistance training is essential to my general health."

  Another participant said of his exercise regimen "I walked briskly 25, 30 minutes a couple times a day, a couple times a week, as well as doing weight-bearing exercises",

which along with a change in diet has resulted in the participant losing weight. The participant commented that family members, coworkers, and friends, all agree that he has had fewer coughing episodes than he had previously.

- Massage: One participant shared that, "I have a therapist who comes every week to massage my back and feel if there is any congestion in my lungs and gets me working again. It has done wonders for me."

- Other non-drug therapies: A participant shared the three things that he found most effective were pulmonary rehab, support groups, and health management coaching given by Alpha Net coordinators. Chiropractic adjustments, said another participant, relieved pressure on his lungs, allowing him to breathe more easily.

Perspectives on an ideal treatment

Participants were asked to identify specific attributes they would look for in an ideal treatment for AATD. They provided a range of perspectives summarized below.

Early Identification and Diagnosis of AATD

A number of participants, commented on the need to have greater public awareness of AATD. Said one "I would like the FDA, or another federal agency, to make a public awareness and public education campaign to all kinds of media, because the Alpha Foundation cannot do it all. . . . It's not a hidden disease, it shouldn't be a hidden disease; it's not even rare. If you consider the heterozygous folks, about 1 in 25 Americans has either homozygous or heterozygous Alpha-1. " One participant commented "We need a registry of Alpha-1 liver affected individuals including children, and including children on the waiting list for transplant, because this is one major impediment to drug development in children with liver disease." Another participant said he fought for early diagnosis "so we can put people on augmentation therapy, or therapy for liver problems, so that we prevent. The key thing we hear now from healthcare is prevention, and we are not really working that hard toward it. Early diagnosis, get them on the proper drugs, the proper treatment, and we prevent the decrease and decline of a person's quality of life." Similarly, another participant commented that, "We take a prick of blood for PKU, from most newborns. . . .Why can't we add the diagnosis of alpha-1 antitrypsin to it? We could save liver people and lung people."

Early Treatment

Many participants strongly advocated early treatment. Said one, "Do we really have to have our loved ones go sick in order to have a transplant? Is there something that can give them ease and comfort from their sick and dying bodies that can be done? The pressure and the anxiety just living in a shell of yourself, I see through my father every day, and it's just not fair." Similarly, a

participant shared that transplantation should be undertaken early. "The person has to be practically at death's door before they get it, and therefore they are less likely to survive it [the surgery]."

Clinical Trial Design for Ideal Treatment

Several participants offered suggestions for clinical trial design improvement. A patient advocate shared his thoughts on the need for a number of different trials including "the need for a post lung transplant augmentation therapy trial, and the need for an augmentation therapy trial in the use of alpha-1 augmentation therapy and non-tuberculosis mycobacteria infections." Another participant advocated that "All studies looking at novel therapeutics for COPD, in general, and liver disease in general, include alpha-1 antitrypsin deficient patients in those studies."

Improved Oxygen Delivery Devices

A number of participants spoke about their desire for better devices to treat AATD that are more portable, easier to use, and effective. One participant commented that she would like to obtain and use liquid oxygen more easily. "I want liquid oxygen for myself, in Massachusetts, but the delivery people, the providers of oxygen, are closing off access to liquid oxygen in Massachusetts. . . . I really would like to have liquid oxygen in my house, instead of depending on the electricity that isn't there, or have to perhaps get an electricity generator to run my oxygen condenser so I can continue living. . . .Why can't we have liquid oxygen here? They have it in Europe." Another participant commented, "There's a whole generation of people who want to invent solutions [to challenges in the delivery of oxygen], and we want you to authorize them and give back to us with your stamp of approval." A participant advocated that "the device manufacturers focus on delivering more effective drug delivery systems and being able to connect that pulse oximetry of a level directly to our oxygen delivery devices so we're getting the right liter flow at the right time when we need it." Similarly, a participant commented on the need for better oxygen delivery device by noting, "There's got to be better devices. There's got to be something that will give you what your blood oxygen is, and would raise or lower the amount of oxygen that you're receiving as result of what the blood oxygen is doing. . . . I'd like to see faster and more advancement in supplemental oxygen."

More Therapeutic Choices

Several participants expressed their desire to have greater diversity of treatments. One participant said "As every single parent in this room that has young children [knows]. . . getting a handle on different medications other than just inhalers for asthma, [is] something [that] needs to be done." A participant suggested that, "We may have therapies using stem cells, or using

genetic therapies that allow us to create the proper alpha-1 antitrypsin. . . . Are there therapies that can help us reverse the causes of our lung disease, and reverse the damage to our lung tissue?"

A Cure

Many participants expressed a strong desire for a cure. One caregiver commented "We don't want to find another augmentation. We don't want to find something that will just help the liver. We want to find a cure and I want to be here one day when we are talking about the approval of a cure for AATD." Another participant shared a similar perspective "We need to find a cure for AATD. Until we find a cure we need treatments for the liver aspect of this disease, and a faster testing and drug approval process so I don't have to. . .lose any more friends to this disease."

One participant commented that, "To me the possibility could be real simple. If we could get … gene therapy or gene modification, make that misfolding thing stop--just let it flush through--maybe then my lungs will get the needed protease inhibitor." Said another participant, "We need a cure, and we need a cure that gives us a future to look forward to, and the cure is going to be in the liver, some type of liver something-or- other is going to give us a better chance. Maybe not for us, but for our children. So we've got to stay motivated."

Other Considerations and Concerns About an Ideal Therapy

Regarding an ideal therapy, one participant commented that, "We need to find a therapy that we can give ourselves. We don't like to have to go to the hospital, or have people come in to give it to us . . . .Give us a form of therapy augmentation if necessary, that we can actually do ourselves, and we'll do it."

However, another participant said that if therapy was easy to self-administer, patients might not be as compliant as they are when they have an appointment with a health care provider. "If you have an appointment every week, or nurse comes to your house, or you have an appointment where you go somewhere, you do it."

Perspectives on participating in clinical trials

FDA was particularly interested in hearing patients' and caregivers' perspectives on participating in clinical trials for potential new treatments. Participants' comments on participating in clinical trials and on communicating about clinical trials are summarized below.

In response to a polling question (Appendix 3, Q19), almost half of participants (or their loved ones) reported participation in some type of clinical trial studying investigational treatments for

AATD. In response to a follow-up question, about half responding participants indicated that they were generally willing to consider participating in a clinical trial if given the opportunity, and another almost equally large percentage said they would be willing, but that it would depend on various factors. Participants shared rich insight into the considerations that affect their decision-making related to clinical trials. The following examples illustrate the perspectives shared.

Willingness to Participate in Clinical Trials

Many participants expressed a willingness to participate in clinical trials without reservation. Said one participant "It would be my honor and privilege to be a part of this effort to find better treatments and eventually a cure for [AATD]. I can't think of a better legacy than to leave this life, having fought to this end." Another participant shared that he enrolled in a research registry and has been part of three research programs in the past. "I'm currently enrolled in the five-year linear liver study. I'm willing to take informed risks to move us toward a cure. My son and his future family are a significant part of my willingness to participate."

Willingness to Participate in Clinical Trials, but Only With Continuation of Current Therapy

A common perspective, shared by many participants, was a willingness to participate in a clinical trial but only if they could maintain their current treatment. One participant said, "We're not in a position to stop effective therapy to be in a trial. And we're not poised to compromise the other organ impacted by this disease to be in a trial. . . .I'm not willing and able and I couldn't ask anyone that I care so deeply about to do bronchoscopies and liver biopsies in excess. There's got to be a way around that in designing trials."

Another participant expressed her reluctance to be in a clinical trial. "I would offer all my history to you, and you can publish it wherever you like, but I don't want you to take away my augmentation. I will take it in any form that you want me to try to take it in, but please don't take it away." Similarly, another participant shared, "There was an opportunity for a clinical trial that I joined, and I had to stop my augmentation for three months. Now I look back at that, and that was a mistake, because in [those] three months I got sick again, whereas I got much better during the first two years of my augmentation. . . . I've had an opportunity to join several trials, and have joined some, and I'll join any trial. . . that does require me to get my augmentation."

Access to Clinical Trials

A number of participants indicated a willingness to participate in a clinical trial if it did not involve much travel. One participant commented that "A lot of people are already compromised with their health and they can't travel to various locations that have the different opportunities

for study." On being in a clinical trial, a participant said "There are folks out there that desperately want to participate, and there's not a lot of clinical trials near us that they can go to. Travel is an issue, finance is an issue, the medicine is an issue, [and] oxygen is an issue. They want to give more, and they are out there and they are hungry."

More Inclusive Clinical Trials

Several participants commented that clinical trials should be more inclusive. Said one, "MZs would love to be in a study; SZs would love to be in a study; almost every study that we have is limited to ZZs. . . .Our community is very willing to participate; give us things to participate in." Another participant shared that, "One thing I'd like to see is more opportunities for children to participate so that we can get some treatments for them. I know it's very difficult, there are ethical issues all around it, but with no option for kids, how else can we get one if we don't provide someone the opportunity to provide a trial. I would sign my children up."

Improving Clinical Trial Design and Protocols

A participant commented that the clinical trial process should be streamlined "My one concern is that we, as a country, seem to have unintentional barriers to research and drug testing. The approval process is lengthy and costly. I ask you today to review this process so that promising tests and treatments are developed [and] can move forward in this country without undue delays and barriers."

Another participant expressed his appreciation about being involved in a clinical trial design and the importance of community engagement. "I wanted to be part of the decision-making. I wanted to be part of the review. . . .I wanted to talk to people about how they were designing their trials and what we needed as a patient community. . . .I sat at that table lending my voice to trial design and what a patient would and would not do, and should and should not do, was important to me and that was my therapy."

Summary of Comments to the Docket

The FDA received a total of 21 submissions to the docket from patients, caregivers and the Alpha-1 Foundation, which are summarized below. Many of the comments to the docket reinforced themes and topics heard at the meeting.

- Six docket commenters shared extensive, vivid descriptions of the lifelong challenges they or their loved ones face with AATD. As one commenter said, "Try to think what it must be like not to be able to breathe, be dependent on oxygen, not be able to do the

simplest of tasks. Think what it must be like to helplessly watch your infant, child or other loved ones suffer from the horrible effects of a failing liver and know the only cure is a liver transplant." Another commenter shared, "My day begins with going to my medicine cabinet and starting my day with all of my inhalers and my meds for the day. If I forget this step I sure can tell. . . I am more short of breath than I normally am. Just getting up and walking to the bathroom with my oxygen on, leaves me gasping for breath. . . . To give you an example of what this feels like, put a straw in your mouth, plug your nose and then walk up a flight of stairs. I wish everyone who did not have lung problems would try this just once. I try to do as much as I can but I sure don't know what I would do without my husband and son."

- Many docket commenters expressed a desire for better therapeutic options. These requests included medications that are not administered so often and have fewer side effects, procedures that are less invasive, new therapy for liver affected patients that will stop damage, and alternatives to transplants. One commenter called for "Medicare to acknowledge and pay for home infusions. Every time an Alpha or other COPD patient enters a hospital we are at risk for infection." Other commentators advocated for the use of medical marijuana (the oil), and for the testing of bavituximab to treat AATD.

- Several docket commenters wanted physicians and patients to be better educated about AATD. Comments included giving people information about new drugs and treatments being researched; informing doctors, especially pulmonologists, about the symptoms of AATD; and encouraging early testing.

- Two commenters expressed their appreciation of current therapy. One commenter wrote, "Medications are very expensive but in my opinion for me it has maintained what lung function I do have left." Another said, "Were it not for my weekly infusions of Prolastin C, I would be dead."

- Several docket commenters advocated for changes in clinical trials. One commenter felt strongly that the "placebo portion of the trial was an incredibly worthless. The loss of time, income, and helpful medication was a great personal inconvenience which would make me really think hard before participating in another study." Another individual wrote that "research studies should be streamlined. Alphas cannot afford to go off therapy to do research studies." "Kids need to be included in research" wrote another commenter.

- One docket commenter wrote about insurance coverage "One of greatest challenges is consistency of coverage and availability of coverage from State to State and insurance company to insurance company."

- Most comments to the docket included a plea to find a cure for AATD.

- The Alpha-1 Foundation submitted their survey[2] of AATD patients, which contained many of the same questions posed at the meeting, and which elicited similar responses.

  The survey and other docket responses can be found at http://www.regulations.gov/#!docketBrowser;rpp=25;po=0;D=FDA-2015-N-1798;dct=PS

Conclusions

This Patient-Focused Drug Development meeting gave government agencies, health care providers, and the drug development industry a rare opportunity to hear directly from patients and their caregivers, about their past and current struggles with AATD, gaps in the management of their diseases, and what they would like to see in the future to allow them to lead more fulfilling lives. FDA is grateful to those who contributed to this meeting, who took the time and effort to present their views, and who had the courage to talk about their personal, and often, painful experiences.

It is clear that, although there have been advances in the development of products to treat AATD, more needs to be done; not only to develop new therapies, optimize the effectiveness of current therapies, and to reduce or eliminate their adverse side effects, but to address broader economic, social, and educational barriers that still remain. The FDA shares the AATD patient community's commitment and desire to further the development of safe and effective drug therapies for AATD.

The perspectives shared at the Patient-Focused Drug Development meeting are highly relevant to FDA regulatory activities. Input from this patient focused workshop has strengthened FDA's understanding of challenges faced by patients with AATD, and will influence FDA's interactions with manufacturers on the development of new therapies and on clinical trial designs. FDA considers these patient and caregiver perspectives when deciding on measures of therapeutic effectiveness, including patient reported outcomes, and when evaluating the benefits versus the risks of new drugs. FDA thanks the patient community for its participation and for its valuable contributions to the understanding of AATD, and the effect of this disease on patients and their families.

[2] FDA has not conducted a review of the design, conduct or analysis of this survey.

Appendix 1: Meeting Agenda and Discussion Questions

Patient-Focused Drug Development for Alpha-1 Antitrypsin Deficiency: Public Meeting

September 29, 2015

8:00 – 9:00 a.m. **Registration**

9:00 – 9:05 a.m. **Welcome**

Donna Lipscomb, Facilitator
Office of Communication, Outreach and Development (OCOD)
Center for Biologics Evaluation and Research (CBER), FDA

9:05 – 9:10 am **Opening Remarks**

Ginette Michaud, M.D.
Deputy Director, Office of Blood Research and Review (OBRR)
CBER, FDA

9:10 – 9:20 a.m. **Overview of FDA's Patient-Focused Drug Development Initiative**

Pujita Vaidya, M.P.H
Office of Strategic Programs
Center for Drug Evaluation and Research (CDER), FDA

9:20 – 9:40 a.m. **Background on Alpha-1 Antitrypsin Deficiency**

L. Ross Pierce, M.D.
Medical Officer, Division of Hematology Clinical Review
OBRR, CBER, FDA

9:40 – 10:00 a.m. **Overview of Discussion Format**

Donna Lipscomb
OCOD, CBER, FDA

Topic 1: The effects of Alpha-1 Antitrypsin Deficiency that matter most to you

10:00 – 10:30 a.m. **Panel Discussion on Topic I**

A panel of patients and caregivers will provide comments followed by a large-group facilitated discussion with participants in the audience.

10:30 -10:35 a.m. **Presentation of Survey Data from the Alpha-1 Foundation**

Elizabeth Johnson, *Alpha-1 Foundation*

10:35 – 11:30 a.m.

Large-Group Facilitated Discussion: Topic 1

Patients and patient representatives in the audience will be invited to contribute to the discussion.

11:30 – 12:30 p.m. **Lunch**

12:30 – 12:35 p.m. **Afternoon Welcome**

Donna Lipscomb
OCOD, CBER, FDA

Topic 2: Patients' perspectives on current approaches to treatments

12:35 – 1:05 p.m. **Panel Discussion on Topic 2**

A panel of patients and caregivers will provide comments followed by a large-group facilitated discussion with participants in the audience.

1:05 – 1:10 p.m. **Presentation of Survey Data from the Alpha-1 Foundation**

Gordon Cadwgan, *Alpha-1 Foundation*

1:10 – 2:00 p.m. **Large-Group Facilitated Discussion: Topic 2**

Patients and patient representatives in the audience will be invited to contribute to the discussion.

Topic 3: Patient perspectives on participating in a clinical trial to study experimental treatments

2:00 – 2:25 p.m. **Large-Group Facilitated Discussion: Topic 3**

Patients and patient representatives in the audiences will be invited to contribute to a discussion on Topic 2 Question 3.

2:25 – 2:30 p.m. **Presentation of Survey Data from the Alpha-1 Foundation**

John Walsh, *Alpha-1 Foundation*

2:30 – 3:00 p.m. **Open Public Comment**

3:00 – 3:15 p.m. **Closing Remarks**

Ginette Michaud, M.D.
Deputy Director, OBRR, CBER, FDA

Discussion Questions

If commenting on behalf of a child or other loved one, please answer the following questions as much as possible from the patient's perspective.

Topic 1: The effects of Alpha-1 Antitrypsin Deficiency that matter most to you

1. Of all of the symptoms that you experience because of your condition, which one to three symptoms have the most significant impact on your life? (Examples may include:
   (a) For lung disease: shortness of breath during specific activities or at rest, chronic sputum, chronic cough, wheezing, weight loss, exacerbations of particular symptoms;

   (b) For liver disease: abdominal pain, loss of appetite, height & weight concerns.)

2. Are there specific activities that are important to you, but that you cannot do at all, or as well as you would like, because of your condition? Please describe, using specific examples. (Examples may include participating in physical activities, attending work/school, and family/social activities.)

3. How have your condition and its symptoms changed over time?

4. What worries you most about your condition?

Topic 2: Perspectives on current approaches to treatment

1. What are you currently doing to treat your condition or its symptoms? (Examples may include:
   (a) For lung disease: inhaled bronchodilators, inhaled corticosteroids, intravenous augmentation therapy with A_1-PI (Human) on a regular or intermittent basis;
   (b) Liver Disease: ursodiol).

   - How well do these treatments work for you?
   - What are the most significant disadvantages or complications of your current treatments, and how do they affect your daily life?
   - How has your treatment changed over time and why?
   - What aspects of your condition are not improved by your current treatment regimen?
   - What treatment has had the most positive impact on your life?

2. If you could create your ideal treatment, what would it do for you (i.e., what specific things would you look for in an ideal treatment)?

3. If you had the opportunity to consider participating in a clinical trial studying experimental treatments, what things would you consider when deciding whether or not to participate?

Appendix 2: FDA and Patient Panel Participants

FDA Panelists

Donna Lipscomb	Office of Communication, Outreach and Development (OCOD), Center for Biologics Evaluation and Research (CBER)
Ginette Michaud	Office of Blood Research and Review (OBRR), CBER
Ross Pierce Howard Chazin Paul Mintz	Division of Hematology Clinical Review (DHCR), OBRR, CBER
Jonathan Goldsmith Larry Bauer	Office of New Drugs (OND), Center for Drugs Evaluation and Research (CDER)
Berkman Sahiner	Office of Science and Engineering Laboratories (OSEL), Center for Devices and Radiologic Health (CDRH)
James Bona	Office of Special Medical Programs (OSMP), Office of Orphan Products Development (OOPD), Office of the Commissioner (OC)
Tony Durmowicz	Division of Pulmonary Allergy and Rheumatology Products, (DPARP), CDER
Rachel Witten	Office of Cell Tissue and Gene Therapy, (OCTGT), CBER
Ruba Mehta	Division of Gastroenterology, and Inborn Error of Metabolism, (DGIEM), CDER

Patient Panelists

Topic 1

Roger Mintz
Jim Quill
Richard Johnson
Henry Moehring
John Walsh
Charlotte Mattison

Topic 2

Jean McCathern
Karen Erickson
Ken Richmond
Marcie Heitzman
Fred Walsh
Jesse Young

Appendix 3: Meeting Polling Questions

Patient-Focused Drug Development for Alpha$_1$ Antitrypsin Deficiency:

Polling Questions

Demographic Questions

1. Where do you live? *<ALLOW ONE RESPONSE>*
    a. Within the Washington, D.C. metropolitan area (including the Virginia and Maryland suburbs)
    b. Outside of the Washington, D.C. metropolitan area, but within the U.S.
    c. Outside of the U.S.

2. Which of the following best describes you? *Check all that apply.* *<ALLOW MULTIPLE RESPONSES>*
    a. I have Alpha$_1$ Antitrypsin Deficiency(AATD) but no active disease
    b. I have emphysema because of AATD
    c. I have liver disease because of AATD
    d. I have both liver disease and emphysema because of AATD
    e. I am a family member or caregiver of someone with AATD

3. What is your/your loved one's age in years? *<ALLOW ONE RESPONSE>*
    a. 0 – 12
    b. 13 – 16
    c. 17 – 49
    d. 50 - 64
    e. 65 or older

4. Are you/Is your loved one: *<ALLOW ONE RESPONSE>*
    a. Male
    b. Female

Question for Topic 1

Ask at beginning of Topic 1 facilitated discussion

5. Which of the following symptoms currently have a significant impact on you/your loved one's daily life? *Check all that apply.* *<ALLOW MULTIPLE RESPONSES>*
    a. Shortness of breath
    b. Chronic cough
    c. Production of phlegm
    d. Poor appetite
    e. Weight loss

f. Weight gain when taking steroids like prednisone
g. Weight gain not related to steroids
h. Anxiety and/or depression
i. Jaundice
j. Chronic itching

6. If you have liver disease because of AATD, how many times in the past year did you/your loved one experience a bleeding episode that required medical attention? *<ALLOW MULTIPLE RESPONSES>*
    a. 0-
    b. 1 – 2 times
    c. 3 or more times

Exacerbations of COPD (Chronic Obstructive Pulmonary Disease, includes Emphysema) Questions

7. How many exacerbations of lung symptoms (shortness of breath, increase in sputum volume or pus content) have you/your loved one had *in the past year*? *<ALLOW ONE RESPONSE>*
    a. 0
    b. 1
    c. 2
    d. 3
    e. 4 or more

8. Of your/your loved one's exacerbations of lung symptoms in the past year, how many required hospitalization? *<ALLOW ONE RESPONSE>*
    a. 0
    b. 1
    c. 2
    d. 3
    e. 4 or more

Questions for Topic 2

Ask at beginning of Topic 2 facilitated discussion

9. In the past year, what therapies have you/your loved used to manage exacerbations of lung symptoms? *Check all that apply.* *<ALLOW MULTIPLE RESPONSES>*
    a. Use of inhalers
    b. Oral antibiotics
    c. Antibiotics given by injection or intravenous (IV) infusion
    d. Oral steroids like prednisone
    e. Steroids like methylprednisolone given by injection or IV infusion
    f. Respiratory treatments administered by a respiratory therapist
    g. Respiratory treatments given by a nebulizer at home

h. Other therapies not listed
i. No treatments

Transplantation Questions

10. Have you/your loved one undergone lung transplantation for emphysema because of AATD? *<ALLOW ONE RESPONSE>*
    a. Yes
    b. No

11. Have you undergone liver transplantation because of AATD? *<ALLOW ONE RESPONSE>*
    a. Yes
    b. No

Augmentation Therapy Questions

12. Are you/your loved one currently receiving augmentation therapy with Alpha1-Proteinase Inhibitor (Aralast NP, Glassia, Prolastin-C, or Zemaira)?
    a. Yes
    b. No

13. If you/your loved one are being treated with augmentation therapy with $Alpha_1$-Proteinase Inhibitor (Aralast NP, Glassia, Prolastin-C, or Zemaira), what is the current frequency of your treatment regimen? *<ALLOW ONE RESPONSE>*
    a. Only treated at the time of exacerbations of COPD
    b. Regular treatment every week
    c. Regular treatment every two (2) weeks
    d. Regular treatment every (4) weeks or less often

14. If you know your $Alpha_1$-Proteinase Inhibitor dose, do you receive a dose higher than 60 mg/kg/week (FDA labeled dose)?
    a. Yes
    b. No
    c. I don't know my dose.

15. Which of the following best describes how you/your loved one feel about your current treatment regimen? *<ALLOW ONE RESPONSE>*
    a. I am satisfied with my current treatment regimen and do not want to change it.
    b. I am satisfied with my current treatment regimen, but am willing to consider new options.
    c. I am not satisfied with my current regimen

16. What is your level of concern regarding the cost of augmentation therapy with $Alpha_1$-Proteinase Inhibitor? *<ALLOW ONE RESPONSE>*

a. Not concerned
b. Mildly concerned
c. Moderately concerned
d. Very concerned

17. If you are not currently on augmentation therapy with Alpha$_1$-Proteinase Inhibitor would you start therapy with an inhaled formulation if one were approved by the FDA? *<ALLOW ONE RESPONSE>*
    a. Yes
    b. No

18. If you are currently receiving augmentation therapy with Alpha$_1$-Proteinase Inhibitor, what factors would influence a decision to possibly switch to an inhaled formulation if one were approved by the FDA? *Check all that apply.* *<ALLOW MULTIPLE RESPONSES>*
    a. Convenience
    b. Tolerability/less discomfort
    c. Efficacy as compared to IV A$_1$-PI on the progression of emphysema
    d. Cost

Ask before discussion on clinical trial.

19. Have you/your loved one ever participated in any type of clinical trial studying investigational treatments for AATD? *<ALLOW ONE RESPONSE>*
    a. Yes
    b. No
    c. I'm not sure

20. If you/your loved one had the opportunity to participate in a clinical trial to study an investigational treatment, which of the following best describes your thoughts? *<ALLOW ONE RESPONSE>*
    a. Yes: I am generally willing to consider participating
    b. No: I would not consider participating
    c. Maybe. My participation would depend on various factors.

21. Would you be willing to participate in a placebo-controlled clinical trial conducted in patients with AATD-related lung disease? *<ALLOW ONE RESPONSE>*
    a. Yes
    b. No
    c. I'm not sure

22. If you were willing to participate in a placebo-controlled clinical trial conducted in patients with AATD-related lung disease, how long would you consider receiving a blinded active test product or placebo? *<ALLOW ONE RESPONSE>*
    a. 3 months or less
    b. 6 months
    c. 1 year
    d. 2 years
    e. 3 years
    f. More than 3 years